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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/242,343	04/12/99	VOLLENBROICH D	2694-119P

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ART UNIT	**PAPER NUMBER**
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/242,343	Vollenbroich et al.
Examiner	**Group Art Unit**
Brenda Brumback	1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3 and 6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Pending claims are 1-12.

Information Disclosure Statement

2. The Information Disclosure Statements filed 04/12/1999 and 05/24/1999 have been entered as Papers # 3 and # 6 respectively. Signed copies are attached hereto.

The information disclosure statement filed 04/12/99 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but German patent DE19521938 referred to therein has not been considered.

Claim Objections

3. Claims 1-12 are objected to because they lack proper introduction. The present Office practice is to insist that each claim be the object of a sentence starting with a phrase such as "I (or we) claim" or "What is claimed is" or "That which is claimed is". See MPEP 608.01 (m). Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivating viruses in biological compositions, such as cell cultures, by contacting the compositions with cyclic lipopeptides in concentrations of less than about 10 to 25 μM , does not reasonably provide enablement for inactivating vises in such compositions using concentrations greater than 70 μM. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claimed invention is drawn to a method of inactivating lipid-enveloped viruses in biological products or in cell cultures by contacting the product with a cyclic lipopeptide at concentrations of 1-100 μM. Vollenbroich et al. (Applied and Environmental Microbiology 63[1]:44-49, 1997) teach that surfactin (a cyclic lipopeptide of claimed formula I) is lethal to cell cultures at concentrations above 70 μM (see the paragraph bridging pages 45 and 46). Based on such teachings, the skilled artisan would be unable to practice the claimed invention using concentrations of cyclic lipopeptides as claimed, absent specific and detailed teachings in the disclosure of how to do so. Such teachings are absent. The specification teaches contacting herpes simplex virus (HSV) with surfactin at a concentration of 80 μM (see Example 5, beginning on page 16); however, the experiment was conducted using virus suspended in culture medium, not virus infecting cell cultures. The specification teaches contacting cells in culture with surfactin at a concentration of 50 μM (see page 26, first paragraph), but does not teach contacting

cell cultures with surfactin at concentrations above 50 μM. Absent such teachings, the skilled artisan would be unable to practice the invention commensurate in scope with the claims, which are drawn to contacting cell cultures with surfactin at concentrations up to 100 μM.

5. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivation of viruses in biological compositions at temperatures below the upper limit of the recited range of 30-60°C, does not reasonably provide enablement for inactivation of viruses in biological compositions at 60°C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claimed invention is drawn to a method of inactivating lipid-enveloped viruses in biological products comprising contacting the product with a cyclic lipopeptide at temperatures of 30-60°C. The disclosure teaches biological products as comprising blood products. Horowitz et al. (Transfusion 25[6]:516-22, 1985; of record in Paper # 6) teaches that heating antihemophilic factor (a blood derivative) in the presence of fatty acid ligands at 60°C results in the complete loss of biologic activity over time (see page 516, first paragraph). Because the art teaches that temperatures around 60°C are deleterious to blood products, detailed teaching of how to practice the claimed invention at the upper limit of the recited range are required to be present in the disclosure. Such teachings are absent. The disclosure teaches that simian immunodeficiency virus (SIV) in albumin is inactivated by treating with surfactin at 60°C (see page 29, first full

paragraph); however it does not teach that the biological activity of the albumin is retained. Absent such teachings in the disclosure, the skilled artisan would be unable to practice the claimed invention commensurate in scope with the claims.

6. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method for inactivation of lipid enveloped viruses; however, claim 1 does not recite active method steps for the process. Claim 1 should be amended something like:

A method of inactivating lipid-enveloped viruses in biological products comprising the steps of

providing a cyclic lipopeptide or a salt or ester of the lipopeptide or a mixture thereof;

contacting said lipopeptide or salt or ester of mixture thereof with the biological product at room temperature for between 30 minutes and 2 hours; ... .

Claim 1 recites biological or biotechnological products or cell cultures. On page 9 of the disclosure, biological products are defined as "products isolated from mammals, such as blood products, products isolated from blood, such as vaccines and plasma derivatives" and biotechnological products are defined as "active substances produced by biotechnological means, such as human proteins...or coagulation factors; however, the invention is not limited to the above-mentioned products from cell cultures". It is unclear from the teachings in the disclosure

what constitutes a biological product vs. a biotechnological product. For example, disclosure teaches vaccines as a biological product isolated from a mammal; however, the art teaches that vaccines are produced by biotechnology. Furthermore, it is unclear how cell culture is to be distinguished from other biological products, as many cell cultures are mammalian in origin. Thus, the metes and bounds of the claimed invention are not clear.

Claim 1 recites the limitation "the serum-free culture medium ... or the serum-containing culture medium" in section b. There is insufficient antecedent basis for this limitation in the claim as the claims does not previously recite either serum-free or serum-containing culture medium.

Regarding claims 2, 6, and 10; the phrase "preferably" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 3 is indefinite because the syntax makes it unclear if any one of naturally occurring, chemically synthesized, or genetically engineered lipopeptides are to be used in the claimed method or whether all are to be used simultaneously.

Comma

A comma should be added to claim 4 (fourth line from the bottom) between "formula I" and "X" to clarify that I designates the overall formula, and that "X" and "Y" designates amino acids within the formula.

Claim 5 is indefinite because it is unclear from the syntax whether C_{11} alkyl or C_{12} alkyl are to be used in addition to the C_{10-12} recited in formula I or whether C_{11} alkyl and C_{12} alkyl are further limitations of the C_{10-12} recited in formula I.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Claim 9 recites the broad recitation "animal", and the claim also recites "human" which is the narrower statement of the range/limitation.

Claim 10 is indefinite in that the syntax of the claim makes it seem that all of the recited viruses are to be inactivated simultaneously with the method of claim 1. Furthermore, all of the viruses should be recited by their full name, rather than by abbreviation only. Lastly, the metes and bounds of "herpesviruses" and "immunodeficiency viruses" cannot be determined, as it is unclear what viruses other than those specifically listed are to be included.

The term "new" in claim 11 renders the claim indefinite as is it is unclear if the claim is drawn to a peptide of formula I or some different or "new" variant thereof.

Claim 12 recites the limitation "lipopeptides" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 11, from which claim 12 depends, recites lipoheptapeptides, not lipopeptides.

Claim 12 provides for the use of the lipopeptides according to claim 11, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

7. Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 1, 3, 4-7, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itokawa et al. (Chem. Pharm. Bull. 42[3]604-607, 1994; or record in Paper # 3),

The claimed invention is drawn to a method of inactivating human or animal lipid-enveloped viruses in biological compositions comprising contacting the composition with a cyclic lipopeptide of general formula 1 (see claim 4), wherein X and Y represent Leu (or either Leu, Ile, or Val in claim 4) and Z represents Val (or Val or Ala in claim 4), or a salt or ester thereof, at a

concentration of between 1 and 100 μM for 30-120 minutes; wherein the lipopeptide is naturally occurring, chemically synthesized, or recombinantly produced; and wherein the virus is selected from HIV-1, among others.

Itokawa et al. teach naturally produced surfactins of general formula, with Leu at positions X and Y (Leu^7) or Leu at position X and Ile at position Y (Ile^7), with Val at position Z, and with either a C_{11} or C_{12} alkyl (see the abstract and Fig. 1, page 605). Itokawa et al. teach that both Leu^7 and Ile^7 surfactin inactivate HIV-1 at concentrations of 1.4×10^{-5} and 2.0×10^{-5} respectively. While, Itokawa et al. do not specifically teach contacting the virus with surfactin for 30-120 minutes, in the absence of evidence to the contrary, the time of contacting would constitute routine optimization of a know test method.

b. Claims 1, 3, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naruse et al. (The Journal of Antibiotics, XLIII(3)267-280, 1990; of record in paper # 3).

The claimed invention is drawn to a method of inactivating human or animal lipid-enveloped viruses in biological compositions comprising contacting the composition with a cyclic lipopeptide or a salt or ester thereof, at a concentration of between 1 and 100 μM for 30-120 minutes; wherein the lipopeptide is naturally occurring, chemically synthesized, or recombinantly produced; and wherein the virus is selected from HSV-1, among others.

Naruse et al. teach a method of inactivating HSV-1 comprising contacting the virus with naturally produced pumilacidin, a cyclic lipopeptide. Naruse et al. teach contacting the virus, the

pumilacidin, and the cell cultures used for assay of virus infectivity simultaneously (see the abstract and the paragraph bridging pages 274 and 275). Although Naruse et al. teach the inhibitory concentration of pumilacidin at between 3.8 and 6.7 μg/ml, rather than as 1-100 μM, in the absence of evidence to the contrary, the concentrations taught by Naruse et al. would be considered to be equivalent to the claimed concentrations. Furthermore, in the absence of evidence to the contrary, determination of the length of time required for virus inactivation would constitute routine optimization of a known test method.

c. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Itokawa et al. or Naruse et al. in view of Horowitz et al.

The claimed invention is drawn to a method of inactivating human or animal lipid-enveloped viruses in biological compositions comprising contacting the composition with a cyclic lipopeptide or a salt or ester thereof, at a concentration of between 1 and 100 μM for 30-120 minutes at temperatures above room temperature or more specifically, at 30-60°C.

As outlined *supra*, both Itokawa and Naruse teach a method for inactivating enveloped viruses in a biological composition comprising contacting the composition with a cyclic lipopeptide. Itokawa et al. teach surfactins containing a β-hydroxy fatty acid and seven amino acids (see page 604, first sentence). Naruse et al. teach pumilacidins composed of a β-hydroxy fatty acid and seven amino acids (see the abstract). Neither Itokawa nor Naruse teaches

contacting the virus to be inactivated with the lipopeptide at temperatures above room temperature.

Horowitz teaches that inactivation of viruses in blood derivatives using a combination of an organic solvent and a detergent is substantially increased by raising the temperature from room temperature (24°C) to 30 or 35°C (see page 520, second full paragraph).

Based on the teaching found in Horowitz that raising the temperature above room temperature accelerates inactivation of viruses, one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have conducted the method described by either Itokawa or Naruse at temperatures above room temperature, in order to more effectively inactivate the viruses.

d. Claims 8, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Itokawa and Naruse in view of Vater et al. (Proceedings 4th European Congress on Biotechnology 3:266-269, 1987).

The claimed invention is drawn to a lipoheptapeptide of general formula 1 (see claim 11), wherein X and Y each represent Ile or Val and Z represents Val and to a method of inactivating human or animal lipid-enveloped viruses in biological products comprising contacting the product with the lipoheptapeptide.

Itokawa et al. teach lipoheptapeptides (surfactins) of general formula 1 produced by *Bacillus subtilis* and *B. subtilis natto*, with Leu at position X, Ile at position Y (Ile^7) and Val at

position Z. Itokawa et al. teach that surfactins inactivate HIV-1. Itokawa et al. differ from the claimed invention in the teaching of Leu, instead of Val or Ile, at position X.

Naruse et al. teach lipoheptapeptides (pumilacidins) of general formula 1 produced by *Bacillus pumilus*, with Leu at positions 2-4 and either Ile or Val at position Y. Naruse et al. teach a method of inactivating HSV-1 with pumilacidins. Although Naruse does not teach Ile or Val at position X and does not teach Val at position Z, he teaches that pumilacidin is one member of a group of acylpeptides (the group also comprising surfactin) which are structurally related and which have various biological activities, including antiviral activity (see page 276, *Discussion*, second paragraph).

Vater et al. teach that lipopeptides produced by *B. subtilis* appear as mixtures of closely related variants with similar amino acid composition that vary considerably in the sequence of their constituents (see page 266, first paragraph). Vater et al. teach that the compounds possess antiviral activity.

Absent evidence to the contrary, the lipopeptides of the claimed invention would be considered to be an obvious variant of the lipopeptides taught by Itokawa et al. One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made the variant lipopeptide with either and Val or Ile substituted at position X in the general formula described by Itokawa et al., as is suggested by the teachings of related lipoheptapeptides with slightly different amino acid compositions that are found in both Naruse et al. and Vater et al. One of ordinary skill in the art at the time the invention was made would have

been motivated to do so in order to make additional antiviral agents and would have had a reasonable expectation of success based on the teachings found in both Naruse et al. and Vater et al. that the structurally related compounds also possess antiviral activity.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
June 16, 2000

Brenda Brumback
Brenda Brumback,
Patent Examiner